Supplementary data

Direct oral anticoagulants vs Vitamin K antagonists in patients with Antiphospholipid Syndrome: systematic review and meta-analysis

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Content

Supplementary data 1 – Search strategy

#	Searches: Cochrane Central Register of Controlled Trials, MEDLINE, PsycInfo
1	exp Antiphospholipid Syndrome/
2	exp Phospholipids/
3	exp cardiolipins/
4	antibodies, antiphospholipid/ or antibodies, anticardiolipin/ or lupus coagulation inhibitor/
5	((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein I) adj5 (auto$ or antibod$ or syndrome or inhibit$)).tw.
6	(APS or APLS or aCLIN).tw.
7	(lupus adj5 (coagulant$ or inhibit$ or antibod$)).tw.
8	Ashersons syndrome.tw.
9	Hughes syndrome.tw.
10	beta 2-Glycoprotein I/ or Glycoproteins/
11	beta 2-Glycoprotein I.tw.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	NOAC.ti,ab.
14	NOACs.ti,ab.
15	DOAC.ti,ab.
16	DOACs.ti,ab.
17	TSOAC.ti,ab.
18	TSOACs.ti,ab.
19	non-vitamin K oral anticoagulant.af.
20	non-vitamin K antagonist oral anticoagulant*.af.
21	direct oral anticoagulant*.af.
22	target specific oral anticoagula*.af.
23	non-vitamin K antagonist oral anticoagulant.af.
24	dabigatran.af.
25	rivaroxaban.af.
26	apixaban.af.
27	edoxaban.af.
28	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	12 and 28
30	remove duplicates from 29

Supplementary data 2 – Late stage/full text exclusion criteria

Study	Exclusion criteria
Noel, 2015	Lack of comparator
Savino, 2015	Authors' experience report
Kunk, 2017	Lack of comparator
Park, 2017	Case series
Malec, 2017	Case series
RISAPS, 2018	Protocol of ongoing trial
ATSTRO-APS, 2018	Protocol of ongoing trial
Hadjiski, 2019	Commentary to Pengo, 2018
Abu-Zeinah, 2019	Lack of intervention and control arms

Supplementary data 3 – TE events

	DOACs n = 43		VKA n = 31	
	Arterial	**Venous**	**Arterial**	**Venous**
Cohen, 2016	0	0	0	0
Goldhaber, 2016	0	3 NA	0	4 NA
Malec, 2019	3 2 MI; 1 S/TIA	7 6 DVT	2 2 S/TIA	10 7 DVT
Martinelli, 2018	3 2 MI; 1 S/TIA	1 1 DVT	1 1 MI	0
Ordi-ros, 2019	11 10 S/TIA	1 NA	3	3 NA
Pengo, 2018	7 3 MI; 4 S/TIA	1 1 DVT	0	0
Sato, 2019	4 4 S/TIA	2 2 DVT	7 6 S/TIA	1 1 DVT
	28 **7 MI; 20 S/TIA**	**15** **10 DVT**	**13** **1 MI; 8 S/TIA**	**18** **8 DVT**

DVT – Deep Vein Thrombosis; NA – Not applicable; MI – Myocardial Infarction; S – Stroke; TIA – Transient Ischemic Attack;

Supplementary data 4 – Subgroup analysis

	TE events	Major bleeding	All bleeding events*	Mortality
Total	RR 1.69 95% CI, 1.09 – 2.62; 6 studies; I^2 = 24%; n = 719	RR 1.22 95% CI, 0.72 – 2.07; 5 studies; I^2 = 0%; n = 691	RR 0.79 95% CI, 0.47 – 1.32; 3 studies; I^2 = 66%; n = 457	RR 1.17 95% CI, 0.48 – 2.84; 4 studies; I^2 = 0%; n = 577
RCTs	RR 2.32 95% CI, 1.14 – 4.72; 3 studies; I^2 = 49%; n = 461	RR 1.03 95% CI, 0.45 – 2.31; 3 studies; I^2 = 0%; n = 461	RR 0.79 95% CI, 0.47 – 1.32; 3 studies; I^2 = 66%; n = 457	RR 1.17 95% CI, 0.48 – 2.84; 4 studies; I^2 = 0%; n = 577
Cohorts	RR 1.32 95% CI, 0.75 – 2.30; 3 studies; I^2 = 7%; n = 258	RR 1.41 95% CI, 0.70 – 2.82; 2 studies; I^2 = 0%; n = 230	Not estimable	Not estimable
p-value	0.22	0.56	NA	NA
High certainty of APS	RR 2.42 95% CI, 1.30 – 4.52; 3 studies; I^2 = 36%; n = 364	RR 1.11 95% CI, 0.49 – 2.50; 3 studies; I^2 = 0%; n = 364	RR 1.00 95% CI, 0.65 – 1.53; 2 studies; I^2 = 30%; n = 306	RR 1.42 95% CI, 0.46 – 4.39; 3 studies; I^2 = 0%; n = 426
Low certainty of APS	RR 1.14 95% CI, 0.61 – 2.16; 3 studies; I^2 = 6%; n = 355	RR 1.32 95% CI, 0.66 – 2.64; 2 studies; I^2 = 0%; n = 327	RR 0.51 95% CI, 0.30 – 0.88; 1 study; I^2 = NA n = 151	RR 0.85 95% CI, 0.20 – 3.65; 1 study; I^2 = NA; n = 151
p-value	0.10	0.75	0.06	0.58
Triple positivity (< 60%)	RR 1.23 95% CI, 0.73 – 2.08; 4 studies; I^2 = 0%; n = 409	RR 1.29 95% CI, 0.66 – 2.50; 3 studies; I^2 = 0%; n = 381	RR 0.61 95% CI, 0.41 – 0.90; 2 studies; I^2 = 0%; n = 267	RR 0.70 95% CI, 0.19 – 2.61; 2 studies; I^2 = 0%; n = 267
Triple positivity (≥ 60%)	RR 3.18 95% CI, 1.36 – 7.46; 2 studies; I^2 = 57%; n = 310	RR 1.12 95% CI, 0.47 – 2.68; 2 studies; I^2 = 0% n = 310	RR 1.19 95% CI, 0.77 – 1.85; 1 study; I^2 = NA n = 190	RR 1.87 95% CI, 0.52 – 6.69; 2 studies; I^2 = 0%; n = 310
p-value	0.06	0.81	0.03	0.30
Just Rivaroxaban	RR 3.36 95% CI, 1.53 – 7.37; 3 studies; I^2 = 22%; n = 338	RR 1.12 95% CI, 0.47 – 2.68; 2 studies; I^2 = 0%; n = 310	RR 1.00 95% CI, 0.65 – 1.53; 2 studies; I^2 = 30%; n = 306	RR 1.42 95% CI, 0.46 – 4.39; 3 studies; I^2 = 0%; n = 426
Other DOACs (+/- Rivaroxaban)	RR 1.08 95% CI, 0.62 – 1.87; 3 studies; I^2 = 0%; n = 381	RR 1.29 95% CI, 0.66 – 2.50; 3 studies; I^2 = 0%; n = 381	RR 0.51 95% CI, 0.30 – 0.88; 1 study; I^2 = NA; n = 151	RR 0.85 95% CI, 0.20 – 3.65; 1 study; I^2 = NA; n = 151
p-value	**0.02**	0.81	0.06	0.58

*random effect, I^2 > 50%.

Supplementary data 5 – GRADE subgroup analysis (RCTs vs Observational)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		VKA	DOACs	**Difference**		
TE events № of participants: 461	**RR 2.32** (1.14 to 4.72)	4.2%	**9.8%** (4.8 to 20)	**5.6% more** (0,6 more to 15,8 more)	⨁⨁◯◯ LOW [a,b]	DOACs may increase the occurrence of thromboembolic events but the evidence is uncertain.
Major bleeding № of participants: 461	**RR 1.03** (0.45 to 2.31)	4.7%	**4.8%** (2.1 to 10.8)	**0.1% more** (2,6 fewer to 6,1 more)	⨁⨁◯◯ LOW [a,c]	DOACs on major bleeding is uncertain.
All bleeding events № of participants: 457	**RR 0.79** (0.47 to 1.32)	32.5%	**25.7%** (15.3 to 42.9)	**6.8% fewer** (17,2 fewer to 10,4 more)	⨁◯◯◯ VERY LOW [a,d,e]	DOACs may decrease the occurrence of all bleeding events but the evidence is very uncertain.
Mortality № of participants: 577	**RR 1.17** (0.48 to 2.84)	2.7%	**3.2%** (1.3 to 7.7)	**0.5% more** (1,4 fewer to 5 more)	⨁⨁◯◯ LOW [a,f]	DOACs on mortality is uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

RCTs - a. 3 RCTs raise some concerns; b. I^2 = 49%; c. RR 1.03 95% CI, 0.45 – 2.31; d. I^2 = 66%; e. RR 0.79 95% CI, 0.47 – 1.32; f. RR 1.17 95% CI, 0.48 – 2.84

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		VKA	DOACs	**Difference**		
TE events № of participants: 258	**RR 1.32** (0.75 to 2.30)	14.5%	**19.1%** (10.9 to 33.3)	**4.6% more** (3,6 fewer to 18,8 more)	⨁◯◯◯ VERY LOW a,b,c	DOACs may increase the occurrence of thromboembolic events but the evidence is very uncertain.
Major bleeding № of participants: 230	**RR 1.41** (0.70 to 2.82)	10.0%	**14.1%** (7 to 28.2)	**4.1% more** (3 fewer to 18,2 more)	⨁◯◯◯ VERY LOW a,d	DOACs may increase the occurrence of major bleeding but the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Observational studies - a. All Observational studies have serious risk of bias; b. I^2 = 7%; c. RR 1.32 95% CI, 0.75 – 2.30; d. RR 1.41 95% CI, 0.70 – 2.82